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ORIGINAL ARTICLE

Head-and-neck paragangliomas are associated with sleep-related complaints, especially in the presence of carotid body tumors

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Abstract

Objectives The carotid body functions as a chemoreceptor. We hypothesized that head-and-neck paragangliomas (HNP) may disturb the function of these peripheral chemoreceptors and play a role in sleep-disordered breathing.

Design This is a case–control study.

Setting This study was conducted in a tertiary referral center.

Participants and main outcome measures We assessed fatigue, sleep, and exercise capacity in 74 HNP patients using three questionnaires (Epworth Sleepiness Scale, St. George Respiratory Questionnaire, and a standard clinical sleep assessment questionnaire). Outcomes were compared to those of age- and sex-matched controls.

Results and conclusions Activity, disturbance of psychosocial function, and total score were worse compared to controls (15.4 ± 18.5 vs. 7.2 ± 9.9 , $P=0.007$; 5.3 ± 10.5 vs. 1.2 ± 2.6 , $P=0.008$; and 10.4 ± 12.9 vs. 5.0 ± 4.8 , $P=0.006$, respectively). Patients reported more daytime fatigue, concentration difficulties, and depression (51% vs. 24%, $P=0.006$; 31% vs. 10%, $P=0.010$; and 19% vs. 2%, $P=0.012$). Waking up was reported to be less refreshing in HNP patients (53% vs. 73%, $P=0.038$). Dysphonia was a predictor of symptoms, activity, disturbance of psychosocial function, and total scores. Remarkably, the presence of a carotid body tumor was an independent predictor of increased daytime sleepiness ($\beta=0.287$, $P=0.029$). In conclusion, patients with HNP have remarkable sleep-related complaints. Especially the presence of carotid body tumors appears to be associated with increased daytime somnolence.

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Keywords Paraganglioma · Glomus tumors · Carotid body tumor · Sleep · SDHD mutation

Abbreviations

HNP Head-and-neck paraganglioma
 CBT Carotid body tumor
 ESS Epworth Sleepiness Scale
 SGRQ St. George Respiratory Questionnaire
 SCAQ Standard clinical assessment questionnaire

Introduction

Head-and-neck paragangliomas (HNP) are highly vascularised tumors originating from neural crest-derived chief cells of the paraganglia belonging to the autonomic nervous

system and are also known as glomus tumors. One of the paraganglia in the neck is the carotid body which normally functions as a peripheral chemoreceptor by registering the arterial oxygen and carbon dioxide (CO₂) concentration [1–7]. HNP are most frequently found in the carotid body region and this subset of paragangliomas is called carotid body tumors (CBT). Paragangliomas can occur in a hereditary context. Familial paraganglioma syndromes are associated with germline mutations in the genes encoding the B, C, and D subunits of mitochondrial complex II succinate dehydrogenase (SDH). These SDH genes may behave as tumor suppressor genes [8–10]. Among these three genes, mutations in SDH-D subunit are the most prominent cause of HNP [11–14].

Although these tumors are usually benign, the location of HNP in close proximity to nerves and vasculature can result in considerable morbidity. Patients often complain of progressive dysphagia, dysphonia, and hearing loss. We recently found that quality of life (QoL) parameters, assessed by validated questionnaires, are reduced in paraganglioma patients [15]. These patients frequently reported fatigue, reduced exercise tolerance, and impaired sleep. This disturbed sleep is of interest since the metabolic ventilatory control system is fine-tuned by two sets of chemoreceptors, the peripheral chemoreceptors in the carotid bodies and the central CO₂ chemoreceptors in the ventral medulla. Bilateral dysfunction of carotid body chemoreceptors causes an abolition of the ventilatory response to hypoxia under normocapnic conditions [16, 17]. The permanent absence of the breathing response to hypoxia and the reduction of central CO₂ sensitivity after bilateral carotid body resection may worsen sleep-disordered breathing [18]. Therefore, the aim of the present study was to specify sleep-related complaints in paraganglioma patients, especially in those with carotid body tumors, using three questionnaires: Epworth Sleepiness Scale (ESS), St. George Respiratory Questionnaire (SGRQ), and a third questionnaire that ensured a standardized clinical assessment of these sleep-related complaints. Patient outcomes of fatigue, sleep, and exercise capacity parameters were compared with an age- and sex-adjusted control group.

Patients and methods

Study protocol

Consecutive patients were recruited from the outpatient clinic of the department of endocrinology in the Leiden University Medical Center, which is a tertiary referral center for HNP. A total of 105 consecutive patients with HNP were asked to participate in this study. The three

questionnaires were sent to their homes in prepaid envelopes. Nonresponders were encouraged by phone to complete and return the questionnaires. Each patient was asked to provide a control person of comparable sex and age. In addition, for every patient, one age- and sex-matched control subject was derived from a database containing results of similar questionnaires in healthy controls in our center [19]. The medical ethics committee of the Leiden University Medical Center approved the study protocol.

Study parameters

Primary study parameters were the results of the three questionnaires. The results were linked to characteristics (age and gender) of the patients; the presence of carotid body tumors, number, size estimate, and location of HNP; surgical procedures; and clinical data. Tumor size was estimated by using the product of the two largest diameters on previous MRI, and patients were subsequently divided into two groups. As a cutoff value in tumor size estimate, we used 8 cm².

Sleep questionnaires

Epworth Sleepiness Scale

The ESS is a validated self-administered questionnaire that has been proposed as a method for measuring daytime sleepiness in adults. The subject is asked to rate on a scale of 0 to 3 the chances he/she would doze in each of eight different situations that are commonly met in daily life (0=would never doze, 3=high chance of dozing). The ESS score is the sum of the eight items score and can range from 0 to 24. The normal range of ESS scores is 2–10 with a normal distribution. A score of 10 or more is considered increased [20, 21].

St. George Respiratory Questionnaire

The SGRQ is a validated self-administered questionnaire that has been proposed as a method for measuring health-related quality of life in chronic respiratory patients. It contains 50 items divided into three subscales: symptoms (8 items), activity (16 items), and disturbance of psychosocial function (26 items). Each item in the questionnaire has a weight attached, which provides an estimate of the distress associated with the symptom or state described. A score can be calculated for each subscale of the SGRQ, and also an overall score can be calculated. SGRQ scores range from 0 to 100, 0 score indicating no impairment of quality of life. A four-point change in SGRQ is considered a clinically significant difference [22].

Standard clinical assessment questionnaire

This questionnaire is frequently used in our hospital as a tool in clinical practice and research. Studies using this questionnaire have been published in peer-reviewed journals [23]. The standard clinical assessment questionnaire (SCAQ) may be used to screen patients for diseases which cause daytime sleepiness like: obstructive sleep apnea syndrome, depression, and restless legs syndrome. The SCAQ contains 12 yes/no items about snoring, loud and irregular snoring, environmental complaints about snoring, apnea, history of cardiovascular disease or hypertension, daytime sleepiness, refreshed when waking up, daytime fatigue, concentration difficulties, dyspnea or restless legs at night, and feelings of depression. In addition, three items on the assessment of bedtime, sleep onset, and rising time are present. Sleep duration and midsleep (clock time halfway during sleep duration) are calculated from sleep onset and rising time.

Statistics

SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL) was used for data analysis. Data are expressed as percentages or as mean \pm SD. We used chi-squared tests, unpaired *T* tests to compare patient and control data, and one-way analysis of variance (ANOVA) to compare several subgroups of patients, when appropriate. Independent variables affecting ESS and SGRQ scores were assessed by using linear regression analysis. These results were expressed as standardized β of independent predictive values. $P < 0.05$ was considered significant.

Results

Patients and controls

A total of 76 of 105 patients (72%) returned the questionnaires, 2 of whom preferred not to participate (Table 1). Thus, 74 completed questionnaires were received (70%). The patient group (53% men) had a mean age of 49 ± 12 years. No significant differences in age, gender, and number of paragangliomas were found between the study population and the patients who did not return or complete the questionnaires.

Of the paraganglioma patients, 40% had one glomus tumor, 23% had two glomus tumors, whereas 37% was diagnosed with three or more tumors. Carotid body tumors were found in 85% of the patients and more than half of these patients had been operated at some point during follow-up. In 40% of HNP patients, one or more carotid body tumors were apparent without the presence of other

glomus tumors. In our study population, eight of these patients had bilateral carotid body tumors (11%). Sixty-one percent was classified as the larger tumor size estimate group. Intra-adrenal paragangliomas (pheochromocytomas) had previously been identified in 11 patients, whereas 2 patients were diagnosed with an extra-adrenal paraganglioma.

Complaints of hearing loss and tinnitus were present in 40% and 34% of the patients, respectively. Dysphonia was present in 18% the patients, and dysphagia was reported by 25% of the patients. Genetic analysis had been performed in 51 of 74 patients (69%). In 49 of these patients, an SDHD mutation was found (96%).

The 76 patients who returned the questionnaires provided 41 controls (54%). The control group (46% men) had a mean age of 45 ± 11 years. There were no significant differences in mean age and sex between patients and controls. For every patient one age- and sex-matched control subject was found in the database to create the larger control group (Leiden controls). The Leiden control group (53% men) had a mean age of 52 ± 9 years.

Sleep-related complaints in patients with HNP

Epworth Sleepiness Scale

No significant difference in daytime sleepiness was present between the group of HNP patients as a whole and the control group on the Epworth Sleepiness Scale (Table 2).

St. George Respiratory Questionnaire

The scores on three of the four subscales of the SGRQ were significantly increased in HNP patients. Activity, disturbance of psychosocial function, and total score were worse in patients compared to own controls (15.4 ± 18.5 vs. 7.2 ± 9.9 , $P = 0.007$; 5.3 ± 10.5 vs. 1.2 ± 2.6 , $P = 0.008$; and 10.4 ± 12.9 vs. 5.0 ± 4.8 , $P = 0.006$). No difference was found in symptom scores. For this questionnaire we did not have an extended control group to include in our analyses, therefore these data are missing in Table 2.

Standard clinical assessment questionnaire

On the standard sleep questionnaire, patients reported more daytime fatigue, concentration difficulties, and symptoms of depression (51% vs. 24%, $P = 0.006$; 31% vs. 10%, $P = 0.010$; and 19% vs. 2%, $P = 0.012$, respectively). They also woke up less refreshed compared to both own controls and the extended control group (53% vs. 73%, $P = 0.038$ and 53% vs. 74%, $P = 0.010$, respectively). Dyspnea, restless legs, and history of cardiovascular disease or hypertension were increased as compared to the own control group (14%

Table 1 Characteristics of head-and-neck paraganglioma patients and controls

		Paraganglioma (<i>n</i> =74)	Controls (<i>n</i> =41)	Leiden controls (<i>n</i> =74)
Age (years)		49.1±12.2	45.0±11.4	52.2±8.9
Sex (male/female)		39/35	18/23	39/35
Height (m)	Male	1.79±0.06		
	Female	1.67±0.08		
Weight (kg)	Male	83±14		
	Female	67±12		
Body mass index	Male	26±4		
	Female	24±5		
1 glomus tumor		29 (40%)		
2 glomus tumors		17 (23%)		
≥3 glomus tumors		27 (37%)		
CBT without other GT		29 (40%)		
Bilateral CBT without other GT		8 (11%)		
Hearing loss		26 (40%)		
Tinnitus		22 (34%)		
Dysphonia		12 (18%)		
Dysphagia		16 (25%)		
Patients tested for mutation		51 (69%)		
SDH-D subunit (D92Y) mutation		49 (66%)		

Table 2 Results of questionnaires in head-and-neck paraganglioma patients

	Paraganglioma (<i>n</i> =74)	Controls (<i>n</i> =41)	<i>P</i> value	Leiden controls (<i>n</i> =74)	<i>P</i> value
ESS					
Total score	6.1±4.1	5.7±3.9	0.555	5.1±3.5	0.092
Total score ≥10	21%	20%	0.867	12%	0.158
SGRQ					
Symptoms score	17.1±19.3	12.2±13.5	0.128		
Activity score	15.4±18.5	7.2±9.9	0.007*		
Disturbance of psychosocial function	5.3±10.5	1.2±2.6	0.008*		
Total score	10.4±12.9	5.0±4.8	0.006*		
SCAQ					
Snoring	66%	54%	0.203	68%	0.816
Loud and irregular snoring	37%	35%	0.865	33%	0.637
Complaints of environment	30%	30%	0.988	29%	0.881
Apnea	16%	10%	0.423	8%	0.176
Cardiovascular disease or hypertension	45%	24%	0.032*	37%	0.348
Daytime sleepiness	39%	25%	0.137	27%	0.127
Waking up refreshed	53%	73%	0.038*	74%	0.010*
Daytime fatigue	51%	24%	0.006*	28%	0.006*
Concentration difficulties	31%	10%	0.010*	7%	0.000*
Waking up at night by dyspnea	14%	0%	0.014*	5%	0.092
Restless legs	34%	12%	0.012*	22%	0.098
Feeling depressed	19%	2%	0.012*	4%	0.005*
Sleep onset	23:28±0:50	23:21±0:54	0.531	23:35±0:58	0.390
Sleep duration	7:18±1:06	7:14±0:58	0.764	7:24±0:58	0.517
Midsleep	3:06±0:42	2:58±0:38	0.317	3:18±0:44	0.116
Rising time	6:44±0:56	6:35±0:41	0.410	7:00±0:48	0.058

ESS Epworth Sleepiness Scale, SGRQ St. George Respiratory Questionnaire, no Leiden controls available for SGRQ, SCAQ standard clinical assessment questionnaire

**P*<0.05

vs. 0%, $P=0.014$; 34% vs. 12%, $P=0.012$; and 45% vs. 24%, $P=0.032$, respectively). However, in comparison to the Leiden control group, no differences were found. The percentage of patients with snoring, apnea, and daytime sleepiness was not significantly different in HNP patients compared to controls. Sleep onset, sleep duration, midsleep, and rising time were also reported equally.

Factors influencing daytime sleepiness in patients with HNP

Age

No significant correlations were found between age and ESS scores or between age and SGRQ scores. Age did increase complaints of dyspnea at night ($\beta=0.572$, $P=0.024$).

Gender

There were no significant correlations between gender and ESS scores or between gender and SGRQ scores. Women reported significantly more complaints of daytime fatigue and restless legs at night in the clinical assessment questionnaire (65% vs. 38%, $P=0.025$ and 46% vs. 23%, $P=0.040$, respectively). Men reported sleep apnea more often (29% vs. 0%, $P=0.001$).

Dysphonia

Dysphonia was present in 18% of the patients. Dysphonia could not be related to a change in ESS scores. However, on the SGRQ, patients with dysphonia had worse symptoms, disturbance of psychosocial function, and total scores (31.8 ± 22.9 vs. 12.7 ± 16.6 , $P=0.002$; 12.8 ± 17.7 vs. 3.9 ± 8.6 , $P=0.029$; and 21.2 ± 21.7 vs. 8.4 ± 10.3 , $P=0.010$, respectively).

Number and estimated size of paragangliomas

Sixty percent of patients had multiple HNP. In addition to snoring and loud or irregular snoring on the standard clinical questionnaire (77% vs. 52%, $P=0.027$ and 47% vs. 22%, $P=0.041$), no other differences were present. The group with larger tumors tended to have more apnea (24% vs. 0%, $P=0.07$) and a higher disturbance of psychosocial function (11.8 ± 16.9 vs. 2.5 ± 5.6 , $P=0.05$). However, the group with the smaller estimates of tumor size reported more daytime sleepiness and fatigue (29% vs. 71%, $P=0.01$ and 41% vs. 79%, $P=0.03$).

Carotid body tumors

Patients with a carotid body tumor reported more complaints of daytime sleepiness on the ESS compared to patients without carotid body tumors (6.6 ± 4.2 vs. 2.6 ± 2.0 ,

$P=0.028$; Table 3). There were no differences when comparing patients with a single carotid body tumor, bilateral carotid body tumors, or multiple tumors including a carotid body tumor. The percentage of patients with an ESS score of 10 or more tended to be increased in paraganglioma patients with bilateral carotid body tumors compared to HNP patients without a carotid body tumor (26.9% vs. 0%, $P=0.068$). In the clinical assessment questionnaires, patients with bilateral carotid body tumors reported more complaints of snoring (82% vs. 40%, $P=0.012$).

Recent catecholamine excess

In total, 14 patients had had at least one catecholamine-positive urine sample in the preceding year. No significant differences between patients with and without catecholamine excess were found in this study.

Surgery

Results in patients with a single CBT are shown in Table 4. Surgical removal of a single CBT was not associated with a different outcome in this study.

Linear regression analysis (multivariate analysis)

Stepwise linear regression was performed in a model including age, gender, dysphonia, difficulties with swallowing, number of HNP, and the presence of carotid body tumors as independent variables and ESS scores and SGRQ scores as dependent variables. Age was an independent predictor of midsleep ($\beta=0.389$, $P=0.005$). Gender was not an independent predictor in this analysis. Dysphonia was found to be an independent predictor of symptoms, activity, disturbance of psychosocial function, and total scores of the SGRQ ($\beta=0.434$, $P=0.001$; $\beta=0.325$, $P=0.043$; $\beta=0.390$, $P=0.015$; and $\beta=0.434$, $P=0.007$, respectively). The presence of a carotid body tumor was an independent predictor of daytime sleepiness ($\beta=0.287$, $P=0.029$) according to the ESS questionnaire. Surgery was not found as an independent predictor.

Discussion

Synopsis of key findings

In this study we investigated daytime sleepiness, common sleep-related complaints, and exercise capacity in patients with HNP using questionnaires. Daytime fatigue, concentration difficulties, waking up less refreshed, and feelings of depression were found more often in HNP patients.

Table 3 Daytime sleepiness in patients with CBT compared to patients without CBT using ANOVA analysis

	No CBT ^a (n=10)	Single CBT ^a (n=35)	P value	Bilateral CBT ^a (n=26)	P value	CBT ^b (n=61)	P value
ESS							
Total score	2.6±2.0	6.6±4.2	0.018*	6.7±4.0	0.019*	6.6±4.1	0.028*
Total ≥10	0%	20%	0.124	26.9%	0.068	23%	0.091
SCAQ							
Snoring	40%	62%	0.222	82%	0.012*	71%	0.054
Apnea	10%	10%	1	22.7%	0.39	15%	0.658

CBT carotid body tumor, ESS Epworth Sleepiness Scale, SCAQ standard clinical assessment questionnaire

* $P<0.05$

^a Other paraganglioma than CBT possibly present

^b CBT present (single and multiple combined) compared to “No CBT”

Remarkably, daytime sleepiness was significantly increased in patients with one or more carotid body tumors, compared to patients without a carotid body tumor. Clinicians need to be aware that carotid bodies may have a distinct role in sleep-related complaints in these patients. However, based on the data of our study, we cannot exclude mechanical airway obstruction to have bearing on our results. Further detailed polysomnographic and ventilatory studies with arterial blood gas analyses in both pre- and postoperative patients would be helpful to further elucidate the pathophysiology.

Comparisons with other studies

Although several studies have investigated clinical presentations of HNP patients, data regarding sleep in these patients are limited. Recently, we performed a QoL study in HNP patients using validated general health-related questionnaires that reported an increase of fatigue and sleep disorders in these patients [15]. Therefore, in the

present study, we included questionnaires that were more specifically designed to assess sleep-related complaints. Daytime fatigue, concentration difficulties, being less refreshed on waking up, and feelings of depression were reported to be worse in patients as compared to controls, thus suggesting an association of HNP and/or its treatment with sleep-related disorders. Dysphonia was found to be an independent predictor of symptoms, disturbance of psychosocial function, and total scores according to the SGRQ, which is concordant with our results in the QoL study.

In HNP patients with one or more carotid body tumors, total scores on daytime sleepiness were significantly higher compared to patients without carotid body tumors. However, using the ESS score of 10 or higher as a cutoff value, a significant difference was only found in patients with bilateral carotid body tumors. In the literature, case reports have been published suggesting associations between carotid body tumors and sleep apnea or hypoventilation [2, 24–27]. Reports have been published describing obstructive sleep apnea syndrome caused by the presence of carotid body tumors with (partial) relief after surgical removal [24, 26]. On the other hand, the development of an abnormal hypoxic ventilatory drive and hypoventilation syndromes after the surgical removal of (bilateral) carotid body tumors has been reported as well [2, 27, 28]. In our study, no significant results concerning the effects of surgery could be found; however, this might be due to the small number of patients that had been operated in our cohort. The percentage of paraganglioma patients in the present study that reported sleep apnea was not significantly increased in comparison with controls. However, in the present study, apnea was only assessed by using self-reported questionnaires and many patients and controls did not know whether or not they had sleep apnea. In addition, although we did not have the exact tumor volumes, our data suggest that sleep apnea may be more

Table 4 Daytime sleepiness and sleep disorders in patients with surgical removal of a carotid body tumor

	Single CBT without surgery (n=10)	Single CBT with surgery (n=11)	P value
ESS			
Total score	5.8±4.7	7.7±4.6	0.353
Total score ≥10	20%	27%	0.696
SCAQ			
Snoring	70%	45%	0.256
Apnea	22%	11%	0.466
Restless legs	30%	27%	0.890

ESS Epworth Sleepiness Scale, SCAQ standard clinical assessment questionnaire

* $P<0.05$

commonly found in those patients who have larger tumors. Considering these observations and the increased daytime sleepiness in patients with carotid body tumors, the results of our study warrant additional sleep apnea studies, like polysomnography, in addition to these self-reported questionnaires.

We did not find a correlation between age and sleepiness by univariate analysis, which is in contrast with findings in the general healthy population [29, 30]. This discrepancy could be due to the limited age range of the subjects included in our study. In the multivariate regression analysis, age was an independent predictor of midsleep. In this study patients were compared with own controls and controls derived from previous studies performed in this hospital. The advantage of using own controls is that they are from the same geographic area and socioeconomic class as the patients [31]. However, there may be a selection bias, because patients could have chosen subjects with a good health status [32]. In addition, a considerable number of control subjects chose to return the questionnaires unanswered, resulting in a relatively small number of own controls. Therefore, for every patient, one age- and sex-matched control subject was derived from a database containing results of similar questionnaires, except for the SGRQ results, in healthy controls in our center.

Respiratory drive during non-rapid eye movement sleep is mainly influenced by the metabolic (autonomic) control system, and therefore chemoreceptors alone may be responsible for providing effective input to the respiratory center in the brain stem [1, 3, 4, 6, 7, 18, 33]. The carotid body is the most powerful peripheral chemoreceptor sensitive mainly to arterial oxygen tension. In response to hypoxia, the firing rate of chemosensory impulses increases in the carotid sinus nerve. The impulses reach the respiratory center in the brain stem via the glossopharyngeal nerve, resulting in an increase in ventilation. In HNP patients the function of these peripheral chemoreceptors may be disturbed, either in the carotid body tumor itself or adjacent nerves. Ventilatory responses to hypoxia may be less adequate [4, 16, 24, 28, 33, 34]. Our results suggest that patients with carotid body tumors have more complaints of daytime sleepiness than patients without carotid body tumors. Thus, we could hypothesize that disturbed chemoreceptor function in HNP patients might be contributory to increased daytime sleepiness, especially in those with carotid body tumors.

Clinical applicability of the study

Of course the hypothesis that dysfunction and/or removal of these carotid bodies (that play a role in controlling breathing) are directly responsible for the impaired sleep is appealing. However, since we did not specifically

investigate airway resistance in our study, we were not able to estimate the contribution of a purely mechanical obstruction of the upper airways to the reported complaints. The dilator muscles of the upper airway have been shown to play a critical role in maintaining patency of the oropharynx during inspiration [35]. Obstructive sleep apnea has been shown to occur in patients with inadequate activity of the genioglossus, the main protrusor muscle of the tongue [36]. Neural output to the genioglossus is stimulated largely by input from the peripheral chemoreceptors [37, 38]. This might be of critical importance to the control of the airway resistance in patients who have undergone surgical removal of carotid bodies. Importantly, larger paragangliomas in situ may also cause direct compression of the upper airway. Interestingly, albeit not significantly, sleep apnea tended to be more frequent in the group with the larger tumors. Unfortunately, we could not precisely calculate tumor volume and did not perform additional studies. This remains to be further analyzed in future studies.

In conclusion, we found self-reported, sleep-related problems to be increased in HNP patients. Remarkably, patients with carotid body tumors had increased daytime sleepiness compared to patients without carotid body tumors. Clinicians need to be aware that carotid bodies may have a distinct role in sleep-related complaints in these patients. However, based on the data of our study, we cannot exclude mechanical airway obstruction to have bearing on our results. Further detailed polysomnographic and ventilatory studies with arterial blood gas analyses in both pre- and postoperative patients would be helpful to further elucidate the pathophysiology.

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